Claims

1. Use of a substance, capable of inducing a physiological estrogen-like effect without interacting with breast cancer cells, in particular without stimulating breast cancer cells, for the preparation of a medicament for the treatment of estrogen deficiency symptoms or diseases of a mammal suffering from or having a high risk of developing breast cancer.

2. Use according to claim 1, wherein the substance is capable of inducing a physiological estrogen-like effect without stimulating breast cancer cells.

3. Use according to any of the preceding claims, wherein the physiological estrogen-like effect is uterine growth as determined by an increase in uterine weight compared to controls after administration of the substance to ovariectomized female athymic nude mice.

4. Use according to any of the preceding claims, wherein the physiological estrogen-like effect is uterine growth as determined by an increase in mean uterine weight compared to controls of at least 0.10 g after administration of the substance to ovariectomized NMRI female athymic nude mice for 8 days.

5. Use according to any of claims 3 or 4, wherein the increase in uterine weight obtained by administration of a dose comparable to a normal dose for the mammal to be treated of the substance corresponds to a weight increase obtainable in the same test animal by estradiol treatment.

6. Use according to any of claims 3 or 4, wherein the increase in uterine weight obtained by administration of a dose comparable to a normal dose for the mammal to be treated of the substance corresponds to a substantially maximum weight increase obtainable in the same test animal by estrogen treatment.

7. Use according to any of the preceding claims, wherein the physiological estrogen-like effect is a change in gonadotropins (FSH and/or LH) as determined by available validated radioimmuno assay techniques.

8. Use according to any of the preceding claims, wherein the physiological estrogen-like effect is a change in cytology of the vaginal cells as determined by cytological counts.

9. Use according to any of the preceding claims, wherein the substance do not interact, in particular stimulate, cancer cells that are estrogen receptor-negative.

10. Use according to any of the preceding claims, wherein the lack of stimulation of breast cancer cells is determined by no effect of the substance compared to a control on growth of the estrogen and progesterone receptor negative MDA-MB-231 (ATCC HTB-26) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth recordings.

11. Use according to any of the preceding claims, wherein the substance do not interact, in particular stimulate, cancer cells that are estrogen receptor-positive.

12. Use according to any of the preceding claims, wherein the lack of stimulation of breast cancer cells is determined by no effect of the substance compared to a control on growth of the estrogen dependent and estrogen receptor-positive MCF-7 (ATCC HTB-22) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth recordings.

13. Use according to any of the preceding claims, wherein the lack of stimulation of breast cancer cells is determined by no effect of the substance when given in combination with estradiol compared to a control on growth of the estrogen dependent and estrogen receptor-positive MCF-7 (ATCC HTB-22) human breast cancer cell line inoculated into six-week-old female athymic nude mice determined when control tumours show increasing size during at least six consecutive growth recordings.

14. Use according to any of the preceding claims for the treatment of estrogen deficiency symptoms or diseases of humans having breast cancer, having a high risk of recurrent breast cancer, or having a risk (such as high risk) of developing breast cancer.

15. Use according to any of the preceding claims, wherein the estrogen deficiency-conditioned symptom or disease is selected from the group consisting of menopausal symptoms; dermatological disorders such as ageing of the skin, wrinkles, dry skin and other

estrogen deficiency related dermatological disorders; dryness of mucous membranes (e.g. vaginal and intestine); brain related disease such as Alzheimer's including other types of dementia; bone and joint related diseases such as osteoporosis, osteochondrosis, osteoarthritis, rheumatoid arthritis, healing of bone fractures, and reduction in skeletal fractures; vaginal estrogen deficiency such as vaginal dryness and dyspareuni; coronary heart diseases such as arteriosclerosis; and disease such as hyperlipidaemia and hypercholesterolaemia.

16. Use according to any of the preceding claims, wherein the estrogen deficiency-conditions symptoms are menopausal symptoms.

17. Use according to any of the preceding claims, wherein the composition is a composition containing substances contained in *Cimicifuga Racemosa* extract, or derivatives thereof.

18. Use according to any of the preceding claims, wherein the composition is or contains *Cimicifuga Racemosa* extract.

19. Use according to any of the preceding claims, wherein the composition is a composition comprising *Cimicifuga Racemosa* plant parts.

20. Use according to any of the preceding claims, wherein the composition is a composition comprising SPP-001.

21. Use according to any of the preceding claims, wherein the composition is a composition containing one or more chemical compounds contained in *Cimicifuga Racemosa* extract, or derivatives thereof.

22. Use according to any of the preceding claims, wherein the composition is combined with a drug which has a selective estrogen receptor modulating (SERM) actitivty.

23. A container comprising a substance according to any of the preceding claims with a pharmaceutically carrier and comprising an indication for relief of estrogen deficiency symptoms without increasing the risk of developing or worsening estrogen dependent cancer.

24. A container comprising a substance capable of inducing a physiological estrogen-like effect without stimulating breast cancer cells with a pharmaceutically carrier and comprising an indication for relief of estrogen deficiency symptoms without increasing the risk of developing or worsening estrogen dependent cancer.

25. A container according to any of the previous claims, wherein the substance is extracted from *Cimicifuga Racemosa*.

26. A method for relieving symptoms caused by estrogen deficiency in a mammal suffering from or having a high risk of developing an estrogen dependent tumour comprising administering to the mammal a substance, capable of inducing a physiological estrogen-like effect without stimulating breast cancer cells.

27. A method according to the previous claim, wherein the mammal is a human.

28. A method for screening for substances or compositions which can be used according to claim 1 or 2, comprising subjecting test substances or compositions to

3) testing for possible estrogen-like effect in normal tissue by measuring increase in uterine weight, changes in gonadotropins, changes in vaginal cytology and/or postmenopausal symptoms in an adult female mammal and
4) testing for possible estrogenic effect in breast cancer, and selecting, as candidates for tissue-selective estrogenic substances or compositions useful in the method according to claim 1 or 2, substances or compositions which,
   c) are capable of inducing physiological estrogenic effects in female mammals, and at the same time
   d) have no effect on the growth of estrogen receptor-negative cancer cells and no effect on estrogen receptor-positive cancer cells in the doses in which they induce physiological estrogen effects.

29. A method according to claim 28, wherein the capability of the substance or composition of inducing physiological estrogen effects e.g. uterine growth female mammals is tested by testing the capability of the substance or composition of effecting uterine weight increase in ovariectomized female NMRI athymic nude mice, the lack of effect of the substance or composition on the growth of estrogen receptor-negative cancer cells is as-

sessed as the lack of capability of the substance or composition of supporting growth of MDA-MB231 xenografts in female NMRI athymic nude mice, and the lack of effect of the substance or composition on the growth of estrogen receptor-positive cancer cells is assessed as the lack of capability of the substance or composition of supporting growth of MCF-7 (ATCC (HTB-22) xenografts in female NMRI athymic nude mice.

30. A method for relieving or curing symptoms or diseases which are caused by estrogen deficiency, or which can be relieved or cured by administration of steroidal estrogen, in a mammal who suffers from breast cancer, or has a risk of recurrent breast cancer, or has a high risk of developing breast cancer,
the method comprising administering, to the mammal, a composition
which has an estrogen-like effect, as evidenced by a capability of the composition of inducing physiological estrogenic effects in adult mammal, and
which is free from interaction with breast cancer cells, in particular free from a stimulating effect on breast cancer,
thereby treating estrogen deficiency symptoms or diseases without introducing a risk of provoking the development of clinically evident breast cancer and/or stimulating growth of existing breast cancer cells in the mammal.

31. A method according to claim 30, wherein the mammal is female mammal.

32. A method according to claim 31, wherein the female mammal is a woman.

33. A method according to any of claims 30-32, wherein the estrogen-like effect possessed by the composition manifests itself in the composition being capable of inducing an increase in uterine weight in adult ovariectomized NMRI female athymic nude mice.

34. A method according to claim 33, wherein the increase in uterine weight following a dose comparable to a normal dose for the mammal to be treated corresponds to a weight increase seen in the same test animal following estradiol treatment.

35. A method according to claim 34, wherein the increase in uterine weight following a dose comparable to a normal dose for the mammal to be treated corresponds to a substantially maximum weight increase obtainable in the same test animal by estrogen treatment.

36. A method according to any of claims 30-35, wherein the estrogen-like effect possessed by the composition manifests itself in the composition being capable of inducing a lowering in FSH and LH in females.

37. A method according to any of claims 32-36, wherein the estrogen-like effect possessed by the composition manifests itself in the composition being capable of inducing an estrogen like change in vaginal cytology in females.

38. A method according to any of claims 30-37, wherein the composition is one which has no effect on the growth of estrogen receptor-negative cancer cells.

39. A method according to claim 38, wherein the composition is one which has no effect on the growth of xenografts of the estrogen and progesteron receptor-negative MDA-MB-231 (ATCC HTB-26) human breast cancer cell line in nude mice.

40. A method according to any of claims 30-39, wherein the composition is one which is free from any effect on breast cancer cells even where the breast cancer cells are documented as being estrogen receptor-positive.

41. A method according to any of claims 30-40, wherein the composition is one which has substantially no agonizing and substantially no antagonizing effect on the effect of estrogen such as estradiol on breast cancer cells, even where the breast cancer cells are documented as being estrogen receptor-positive.

42. A method according to claim 41, wherein the composition is one which substantially does not bind to estrogen receptors of cancer cells.

43. A method according to any of claims 40-42, wherein the composition is one which has no effect on xenografts of the estrogen receptor-positive and estrogen dependent MCF-7 (ATCC HTB-22) human breast cancer cell line in nude mice, as evidenced by the composition having no growth supportive effect and no growth inhibitory effect on the xenografts whether given alone or in combination with estradiol.

44. A method according to claim 43, wherein the composition is one which has no effect on xenografts of the estrogen receptor-positive and estrogen dependent MCF-7 (ATCC HTB-22) human breast cancer cell line in nude mice, as evidenced by the composition having no growth supportive effect and no growth inhibitory effect on the xenografts whether given alone or in combination with estradiol, even where the composition is administered in a dose which is 10 or even 100 times higher than a dose giving, in the same strain of nude mice, a maximum uterus weight increase.

45. A method according to any of claims 30-44, wherein the estrogen deficiency-conditioned symptom or disease is selected from the group consisting of menopausal symptoms, dermatological disorders such as ageing of the skin, dryness of mucous membranes (e.g. vaginal and intestine), brain related disease such as Alzheimer's including other types of dementia, bone and joint related disease such as osteoporosis, osteochondrosis, osteoarthritis, rheumatoid arthritis, healing of bone fractures, and reduce in skeletal fractures and disease such as hyperlipidaemia, hypercholesterolaemia, arteriosclerosis.

46. A method according to claim 45, wherein the estrogen deficiency-conditions symptoms are menopausal symptoms.

47. A method according to any of claims 30-46, wherein the composition is a composition containing substances contained in *Cimicifuga Racemosa* extract, or derivatives thereof.

48. A method according to claim 47, wherein the composition is or contains *Cimicifuga Racemosa* extract.

49. A method according to claim 47, wherein the composition is a composition comprising *Cimicifuga Racemosa* plant parts.

50. A method according to claim 47, wherein the composition is a composition comprising SPP-001.

51. A method according to claim 48, wherein the composition is a composition containing one or more chemical compounds contained in *Cimicifuga Racemosa* extract, or derivatives thereof.

52. A method according to claim 30, wherein the composition is combined with a drug which has a selective estrogen receptor modulating (SERM) activity.